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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/710,339	11/09/2000	Henrik Bisgard-Frantzen	5835.200-US	9183

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EXAMINER	
MONSHIPOURI, MARYAM	
ART UNIT	**PAPER NUMBER**
1652	16

DATE MAILED: 07/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Application No.	Applicant(s)
09/710,339	Bisgard-Frantzen et al.
Examiner	**Art Unit**
Maryam Monshipouri	1652

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If no period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *31-49* is/are pending in the application.

4a) Of the above, claim(s) *34-38, 44-47, and 49* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *31-33, 39-43, and 48* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *7, 10, 1.*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Application/Control Number: 09/710,339

Art Unit:

Applicant's response to restriction requirement filed 6/7/2002 (Paper #15) is acknowledged. Applicant elected Group I invention directed to Fungamyl-like alpha amylase variants and compositions comprising said variants without traverse.

Claims 1-30 are canceled. Claims 31-33, 39-43 and 48 are under examination on the merits.

Claims 34-38, 44-47 and 49 are withdrawn as drawn to non-elected invention.

Claim Objections

1. Claim 31(b) is objected to because of the following informalities: the term " region position" in clam 31 part (b) is confusing. Applicant is advised to insert the term "or" between "region" and "position". Appropriate correction is required.

Claim Rejections - 35 USC § 112

2.The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "Q153S" is unclear. The examiner cannot see this amino acid, namely glutamine at position 153 of SEQ ID NO:2. Currently SEQ ID NO:2's 153 position is occupied with Aspartic acid.

4. ***Claim Rejections - 35 USC § 102***

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 31 is rejected under 35 U.S.C. 102(b) as being anticipated by JP07177891, Jul 1995. Said patent teaches a mature form of an alpha amylase that comprises an alteration in the region 98-110 of SEQ ID NO:2 wherein residues 99 and 104 are substituted, prior to this invention.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 31-33, 39-43 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Christianson (U.S. Patent No. 6,136,553, 11/2000) in view of Matsuura et al. (J. Biochem., 95, 697-702, 1984) further in view of Svendsen et al. (WO 96/23874, 8/1996, cited in the IDS). Christianson teaches and claims a method of identifying amino acid sites in a target protein which

affect the stability of the target protein comprising (1) inputting the three dimensional coordinates of said target protein into a computer, (2) generating a probe-accessible surface of said target protein (3) identifying the amino acids which make up the boundaries of internal cavities which affect the stability of the protein, (4) mutating at least one of the sites to create a mutant target protein (5) expressing and isolating the mutant target protein and testing the mutant target protein for stability (see claims 1-2). Christianson does not use alpha amylase, set forth as SEQ ID NO:2 of this invention, as target protein.

Matsuura teaches the complete amino acid sequence of Aspergillus oryzae, matching SEQ ID NO:2 of this invention completely, as well as its three dimensional crystal structure.

At the time the invention was made it would have been obvious to one of ordinary skill in the art to start with the method of Christianson and replace its target protein with alpha amylase of Matsuura whose crystal structure is known using the following teachings of Svendsen as a guide in order to find regions within the structure of alpha amylase which can be mutated in order to result in a more stable or heat resistant amylase variant: Svendsen in page 1 teaches that almost all alpha amylases have a few conserved regions with approximately the same length and spacing. One of these regions resembles calcium binding site and the others are thought to be necessary for active center and/or binding of the substrate. According to Svendsen hybrid amylases may be prepared wherein certain loop regions of termamyl amylase may be replaced with equivalent loop regions (identified by sequence and crystal structure comparisons) of amylase from Aspergillus source such as SEQ ID NO:2 of this invention (see pages 8-14). In page 36 Svendsen also teaches

that termamyl alpha amylase structure contains a number of unique internal holes, which may contain water and a number of cervices. It further indicates that in order to increase the thermostability of the amylase it may be desirable to reduce the number of holes and crevices by introducing bulkier residues, in the vicinity or surroundings of the hole (see pages 36-40). Svendsen then teaches a series of variants including S151 (see page 38), V259, F284 (see page 39) and L427, V481 (see page 40) which could be good candidates for mutation resulting in more thermostable amylase variants.

Svendsen also indicates that (see page 57) that its amylase variants may be useful in production of sweeteners and ethanol from starch imply preparing maltose syrups and brewing compositions comprising amylase variants. In addition immobilized preparation of enzymes such as glucose isomerase for the preparation of fructose syrup is also suggested by Svendsen.

One of ordinary skill in the art is motivated to prepare variants in which residues equivalent to, for example, S151, V259, F284 and L427 of Svendsen which are located in regions equivalent to region 161-167 and region 468-475 of SEQ ID NO:2 of this invention are mutated because mutating such equivalent residues will result in products that can be used in either free or immobilized form (prepared by methods similar to those applied to glucose isomerase, see page 57 of Svendsen) in fermentation, sweetener preparation and baking etc. tolerating higher temperatures, rendering amylase variants more useful and desirable of commercial applications.

Further one of ordinary skill in the art has a reasonable expectation of success in mutating amylase of this invention at equivalent positions to, for example, S151, V259, F284 and L427 of

termamyl like alpha amylases because the crystal structure of SEQ ID NO:2 of this invention is known and methods of identifying amino acid sites in target proteins (including amylases), their homologs and/or equivalents as well as methods of preparing mutant amylase products using site directed mutagenesis techniques are well established in the prior art, rendering the invention obvious.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Maryam Monshipouri, Ph.D. whose telephone number is (703) 308-1083.

The Examiner can normally be reached daily from 8:30 A.M. to 5:00 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. P. Achutamurthy, can be reached at (703) 308-3804. The OFFICIAL fax number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

M. Monshipouri

Maryam Monshipouri, Ph.D.

Patent Examiner